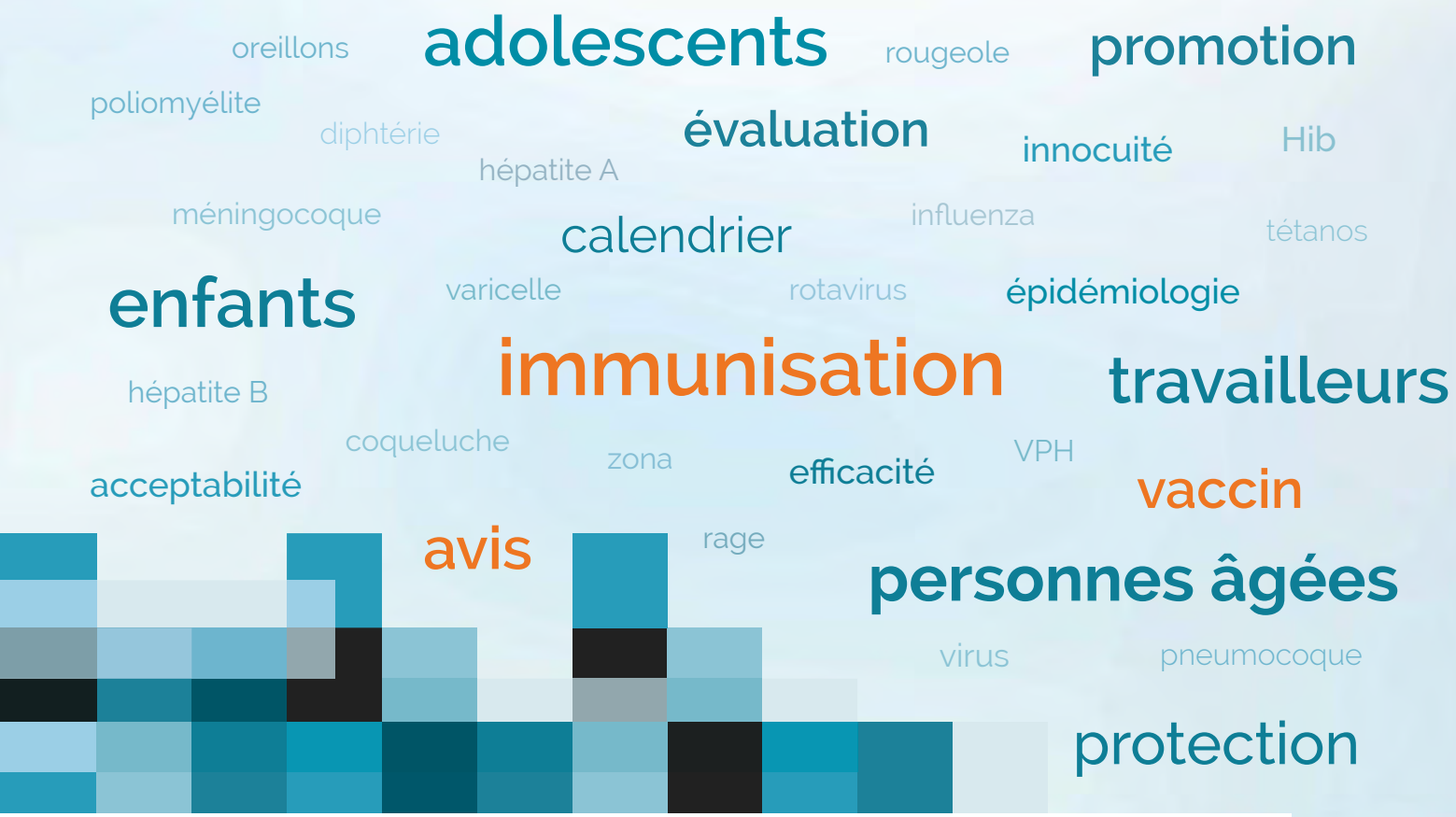
INSPQ
INSTITUT NATIONAL
DE SANTÉ PUBLIQUE
DU QUÉBEC



Scientific advisory on the optimal schedule for childhood immunization against pneumococcal disease in Québec

COMITÉ SUR L'IMMUNISATION DU QUÉBEC

Québec

Scientific advisory on the optimal schedule for childhood immunization against pneumococcal disease in Québec

COMITÉ SUR L'IMMUNISATION DU QUÉBEC

Direction des risques biologiques et de la santé au travail

September 2017

Institut national de santé publique Québec

AUTHOR

Comité sur l'immunisation du Québec (CIQ)

REDACTOR

Philippe De Wals, Département de médecine sociale et préventive, Université Laval, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

COLLABORATORS

Rachid Amini, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Geneviève Deceuninck, Axe de recherche immunologie-infectiologie, CHU de Québec

Brigitte Lefebvre, Laboratoire de santé publique du Québec, Institut national de santé publique du Québec

Zhou Zhou, Axe de recherche immunologie-infectiologie, CHU de Québec

LAYOUT

Marie-France Richard, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Legal Deposit – 2nd quarter 2018
Bibliothèque et Archives nationales du Québec
ISBN: 978-2-550-80168-9 (French PDF)
ISBN: 978-2-550-81128-2 (PDF)

Comité sur l'immunisation du Québec (CIQ)

Active members

Julie Bestman-Smith, Centre hospitalier affilié universitaire de Québec, Hôpital de l'Enfant-Jésus

François Boucher, Département de pédiatrie, Centre mère-enfant Soleil, Centre hospitalier universitaire de Québec (CHUQ-CHUL)

Nicholas Brousseau, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec, Direction de santé publique du Centre intégré universitaire de santé et de services sociaux de la Capitale-Nationale

Alex Carignan, Département de microbiologie et d'infectiologie, Université de Sherbrooke

Gaston De Serres, Département de médecine sociale et préventive, Université Laval, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Philippe De Wals, Département de médecine sociale et préventive, Université Laval, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Rodica Gilca, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Vladimir Gilca, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Maryse Guay, Département des sciences de la santé communautaire, Université de Sherbrooke, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Caroline Quach, CHU Sainte-Justine, Département de microbiologie, infectiologie et immunologie, Université de Montréal

Chantal Sauvageau, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec, Département de médecine sociale et préventive, Université Laval

Bruce Tapiéro, Service des maladies infectieuses, Centre hospitalier universitaire Sainte-Justine, Université de Montréal

Liaison members

Dominique Biron, Fédération des médecins omnipraticiens du Québec, Clinique pédiatrique Sainte-Foy

Marjolaine Brideau, représentante des vaccinatrices du terrain et des services de proximité des CISSS/CIUSSS, Centre intégré de santé et de services sociaux de Lanaudière

Ngoc Yen Giang Bui, Comité consultatif québécois sur la santé des voyageurs, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Hélène Gagné, représentante de la Table de concertation nationale en maladies infectieuses, Centre intégré universitaire de santé et de services sociaux du Saguenay–Lac-Saint-Jean, Direction de santé publique

Catherine Guimond, représentante, Ordre des infirmières et infirmiers du Québec, Centre intégré de santé et de services sociaux de la Montérégie-Centre

Marc Lebel, Association des pédiatres du Québec, Centre hospitalier universitaire Sainte-Justine

Céline Rousseau, Association des médecins microbiologistes infectiologues du Québec, Hôpital du Suroît

Ex officio members

Marc Dionne, Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec

Monique Landry, Direction générale adjointe de la protection de la santé publique, ministère de la Santé et des Services sociaux

Richard Marchand, Laboratoire de santé publique du Québec, Institut national de santé publique du Québec

Eveline Toth, Direction générale adjointe de la protection de la santé publique, ministère de la Santé et des Services sociaux

Bruno Turmel, Direction générale adjointe de la protection de la santé publique, ministère de la Santé et des Services sociaux

Table of contents

List of tables and figures

List of abbreviations and acronyms

AOM	Acute otitis media
CIQ	Comité sur l'immunisation du Québec
IPD	Invasive pneumococcal disease
IR	Incidence rate
MSSS	Ministère de la Santé et des Services sociaux
OPA	Opsonophagocytic activity
PCV7	7-valent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
RAMQ	Régie de l'assurance maladie du Québec (Québec Health Insurance Plan)
RD	Reportable diseases
VE	Vaccine efficacy

Summary

The childhood immunization program was implemented in Québec to reduce the burden of pneumococcal disease, with the primary objective of lowering the incidence of invasive pneumococcal disease (IPD). The program began in 2002, targeting children with a high risk of IPD, and in 2004 it became a universal program for all children under age five. A schedule of four doses (3+1) is recommended for high-risk children and three (2+1) for other children.

The initial 7-valent pneumococcal conjugate vaccine (PCV7) was replaced by the 10-valent vaccine (PCV10) in 2009, and then by the 13-valent vaccine (PCV13) in 2011. Since the program began, immunization coverage rates have been high: over 90% of children receive the recommended number of doses. At the request of the Ministère de la Santé et des Services sociaux du Québec (Ministry of Health and Social Services, or MSSS), the Québec Immunization Committee (CIQ) prepared an scientific advisory regarding the choice of an optimal schedule that takes into account dimensions mentioned in the analytical framework proposed by Erickson and collaborators (2005).

The data available indicate that the direct protection against IPD caused by the serotypes contained in PCV13 is not much different in schedules that include only PCV10 or PCV13, despite the fact that PCV13 includes three serotypes that are absent from PCV10 (3, 6A and 19A). PCV10 confers cross-protection against serotype 19A and 6A IPD. The efficacy of PCV13 in preventing IPD caused by serotype 3 seems to be low and of short duration, even non-existent in certain studies. A mixed schedule of two doses of PCV10 for the initial immunization and one dose of PCV13 for the booster may provide protection very similar to that obtained with a schedule that includes only PCV13.

Despite evidence of the immunogenicity of PCV10 against serotype 19A, and the cross-protection it confers, the advantage of a schedule that includes one PCV13 dose is that it provides reassurance regarding the reduced transmission of this serotype to the entire population, by inducing herd immunity. Based on immunogenicity data, it can be assumed that a mixed schedule would strengthen and prolong protection against serotype 19A IPD, while maintaining the herd immunity acquired with the current schedule.

The differences between the various schedules in terms of direct and indirect protection against IPD caused by the 13 serotypes included in PCV13 could be offset by a phenomenon of differential replacement. As demonstrated by the experience in Sweden, this would translate into a higher incidence of non-vaccine serotypes when a schedule including only PCV13 is used, and result in zero effect on IPD incidence caused by all serotypes.

Regarding protection against pneumonia and acute otitis media (OM), there is no compelling evidence to confirm the superiority of one schedule or another. There is a possibility that a schedule that includes PCV10 could be slightly more efficient in reducing the burden of otitis and that a schedule that includes PCV13 could be slightly more efficient in reducing the burden of all-cause pneumonia.

Both vaccines are safe, although PCV10 is slightly less reactogenic. A potential disadvantage of a schedule that uses PCV13 is an inferior immune response against pneumococcus among infants whose mothers received the diphtheria, tetanus and pertussis vaccine during pregnancy.

Assuming that the acquisition cost of the PCV13 vaccine is substancially higher than that of PCV10, an economic evaluation shows that, in most plausible scenarios, a mixed schedule or a schedule including only PVC10 would be more cost-efficient than a schedule that includes only PCV13.

On the local level, it is more difficult to manage a mixed schedule that includes both vaccines than a single-vaccine schedule. However, the number of errors could be minimized with the training opportunities usually available. In the event that a mixed schedule is chosen, administering one vaccine instead of the other should, in all likelihood, pose no major risk.

Certain healthcare professionals prefer vaccines that contain a maximum of serotypes since this makes it possible to minimize the theoretical risks of an inadequate control of serotype 19A with a program that includes only PCV10. A mixed schedule that includes PCV13 for the booster would provide some reassurance to those who prefer this vaccine.

To conclude, the three schedules assessed in this scientific advisory may be justified and none can be unequivocally rejected. The 2+1 PCV10 and 2+1 PCV13 schedules are used in numerous developed countries and a mixed schedule cannot be inferior to the former. The two greatest uncertainties hindering the decision-making process are the number of additional IPD cases that could possibly occur in children using a 2+1 PCV10 or a mixed schedule, versus the current PCV13 schedule, and the price difference between these two vaccines. The cost-efficiency ratios of the different scenarios are adjusted using a combination of these two parameters. If it is considered that there is no or little difference in the number of IPD cases, the 2+1 PCV10 is the most efficient option, assuming the unit price is less than that of the PCV13. In most scenarios, the mixed schedule is an economically enticing option compared with the 2+1 PCV13 schedule. The primary advantage of the mixed schedule would be to maintain the gains attained using the current schedule in terms of reducing the burden of the illness and preventing the risk of a rise in the incidence of serotype 19A in the entire population. The current schedule should be maintained if the cost difference between the two vaccines is low.

Should uncertainty remain regarding the price and purchase conditions of the vaccines, it seems sensible to not make a univocal recommendation and to let the Ministère de la Santé et des Services sociaux make a final decision based on its priorities and the proposed prices. If it is not possible to negotiate the purchase of vaccines for a mixed schedule and if the only options are to either maintain the current 2+1 PCV13 schedule or to choose a 2+1 PCV10 schedule, another consultation should take place.

Whatever the decision, active and ongoing monitoring of the epidemiology of IPD and hospitalizations must continue. Should any changes occur, the CIQ could revise its scientific advisory and adapt the program accordingly.

A supplementary scientific advisory regarding the recommended schedule for high-risk groups including children living in Québec’s northern regions will be written at a later time.

1 Introduction

At the request of Québec's national public health director, the Comité sur l'immunisation du Québec (CIQ), which reports to the Institut national de santé publique du Québec (INSPQ), was asked to provide an scientific advisory on the relevance of changing the schedule for childhood immunizations against pneumococcal disease. This request is motivated by the availability of new data on the efficacy of these two currently available vaccines, and of a mixed schedule combining the two vaccines. The purchase price of these two vaccines may also be different, which could lead to significant budgetary implications. The scientific advisory was written taking into consideration the analytical framework of immunization programs proposed by Erickson and collaborators (1). It is based on an exhaustive review of documents including volumes, reports, published articles and presentations made during conferences. A systematic review of scientific publications from 2010 to 2015 carried out under the auspices of the World Health Organization is the best current reference on the effects of the two second-generation pneumococcal conjugate vaccines (2). This source is quoted extensively. The scientific advisory was discussed during two CIQ plenary meetings and the final version was approved on September 15, 2017.

2 Background

The composition of the three pneumococcal conjugate vaccines approved for use in children in Canada is detailed in Table 1. Only the last two are currently marketed.

Table 1 Pneumococcal conjugate vaccines licensed in Canada

Vaccine	Manufacturer	Pneumococcal polysaccharides	Carrier protein
PCV7 Prevnar®	Pfizer	4, 6B, 9V, 14, 18C, 19F, 23F	CRM_{197}
PCV10 Synflorix®	GSK	1, 4, 5, 6B, 7F, 9V, 14, 18C*, 19F**, 23F	Protein D TT[1] DT[2]
PCV13 Prevnar13®	Pfizer	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	CRM_{197}

[1] Tetanus toxoid; [2] Diptheria toxoid.

Pneumococcal disease, including invasive disease, pneumonia and otitis, represents a health burden that justified the implementation of an immunization program for children in Québec(3). In 2002, the Ministère de la Santé et des Services sociaux du Québec decided to offer the first seven-valent pneumococcal conjugate vaccine (PCV7) free of charge to children under age five with an increased risk of invasive pneumococcal disease (IPD), according to a four-dose schedule (3+1). Since then, the vaccine has also been offered to children under age five living in the two Northern Québec health regions with concentrated Cree and Inuit populations. In December 2004, PCV7 was offered for free to all newborns not at a high risk of invasive disease using a schedule of three doses (2+1) administered at 2, 4 and 12 months respectively. At the same time, a catch-up approach was offered for children under age five as part of routine visits. The program's initial objective was to reduce by 60% the average annual incidence of IPD in children aged six months to two years (4). This objective, expressed quantitatively, was not discussed in the last update of the Programme national de santé publique, but serves as a reference (5).

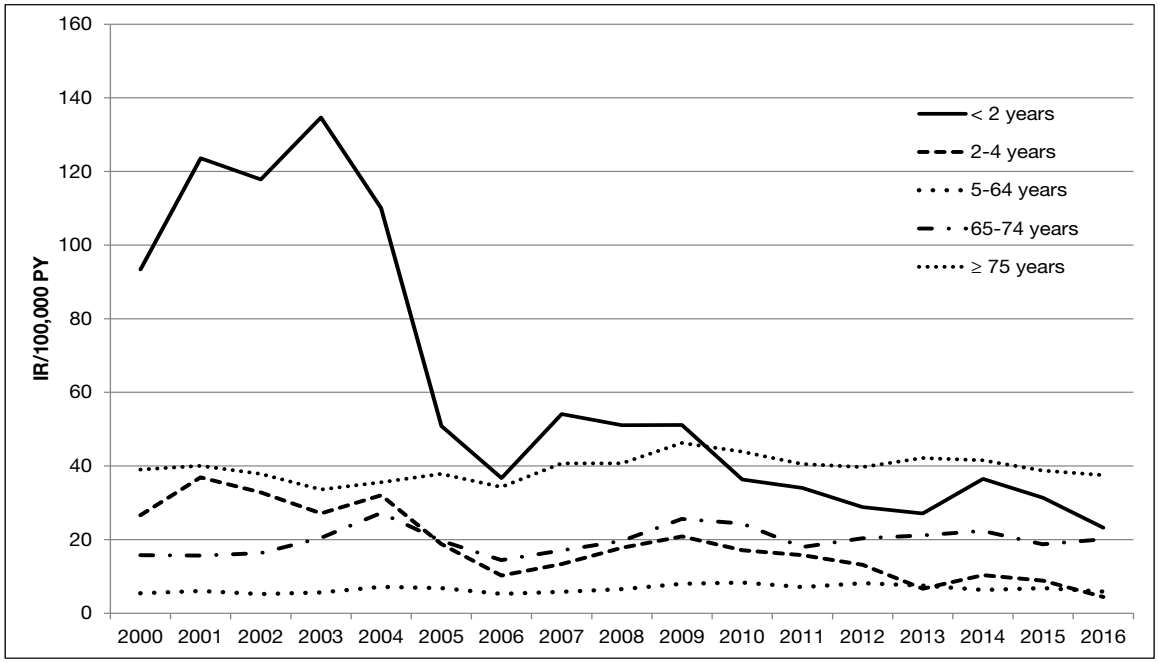
In 2009, a 10-valent vaccine (Synflorix® or PCV10), including three additional serotypes, replaced the PCV7 in routine childhood immunizations, without a catch-up. In 2011, the 13-valent vaccine (Prevnar13® or PCV13) replaced the PCV10, with no catch-up. Since the universal program began in 2004, immunization coverage among the target population has been high and has remained stable (6). In a childhood immunization coverage survey conducted in Québec in 2014, approximately 2% of parents reported that their child had not received a pneumococcal vaccine, while 93% of children had received the recommended number of doses (7). Among vaccinated children aged two, 93% had received the booster on time, i.e. between 15 and 23 months, which demonstrates good adherence to the recommended schedule.

3 Epidemiological situation

3.1 Invasive disease

The evolution of the incidence rates of invasive pneumococcal disease, established using the registry of notifiable diseases, is represented in Figure 1. A significant reduction in the incidence in children under age two and those between the ages of two and four is noted following the introduction of PCV7 in 2004. In these age groups, a slight increase is noted from 2007 to 2009, followed by another reduction with the introduction of PCV10 in 2009 and PCV13 in 2011, with a transitional rebound in 2014. In the other age groups, a slight decrease in incidence is observed following the introduction of the first vaccine in the routine immunization of all children in 2004, and the introduction of the two others, in 2009 and 2011. However, there was virtually no change in the overall incidence of invasive disease during the entire observation period for all individuals aged five years and over.

Figure 1 Incidence rate (per 100,000 person-years) of invasive pneumococcal disease in Québec according to age, 2000–2016



Source: Directory of reportable diseases.

Table 2 provides detailed information on the distribution of serotypes identified in young children by the Québec Public Health Laboratory (QPHL) during the 2005–2015 period and collected from all the microbiology laboratories of acute care hospitals. Following the widespread use of PCV7, the serotypes included in the vaccine quickly diminished. The same observation was made with the introduction of PCV10 in 2009 and PCV13 in 2011. In recent years, the number of cases caused by all PCV7 serotypes, including serotype 6A, is one per year on average. The first serotypes that emerged after the replacement of PCV7 were 7F and 19A. Following the introduction of PCV10 in 2009, the incidence of IPD caused by serotypes 7F and 19A declined and continued to do so when PCV13 was introduced in 2011. Currently, serotype 7F has virtually disappeared, but serotype 19A persists among children between the ages of two and four years. Serotype 1 is uncommon among children and has disappeared with the introduction of new-generation vaccines covering this serotype.

Table 2 Strains isolated in children under age five with invasive pneumococcal disease in Québec, 2005–2016

Age groups	Serotypes	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
0–5 months	PCV7	7	4	1	1	2	1	0	0	1	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0
	3	1	0	1	1	0	1	0	2	1	0	0	0
	7F	2	3	3	1	2	3	2	1	0	1	0	0
	19A	0	2	1	3	5	6	4	1	1	1	0	1
	Other	2	3	6	4	3	1	5	3	3	9	2	1
	Subtotal	**12**	**12**	**12**	**10**	**12**	**12**	**11**	**7**	**6**	**11**	**2**	**2**
6–11 months	PCV7	8	3	5	1	1	1	0	0	0	1	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0
	3	1	2	0	0	0	1	1	0	0	0	0	0
	7F	0	2	1	2	5	0	0	0	0	0	0	0
	19A	3	3	7	13	11	6	3	7	2	2	1	1
	Other	2	5	14	10	7	6	5	3	8	11	10	6
	Subtotal	**14**	**15**	**27**	**26**	**24**	**14**	**9**	**10**	**10**	**14**	**11**	**7**
12–23 months	**PCV7**	**27**	**7**	**1**	**1**	**0**	**1**	**0**	**1**	**0**	**0**	**1**	**1**
	1	0	0	0	0	1	0	0	0	0	0	0	0
	3	1	1	1	2	3	0	1	2	0	0	0	2
	7F	0	1	4	2	9	1	2	0	0	0	0	0
	19A	5	6	15	22	27	22	9	4	4	0	1	3
	Other	12	12	18	17	16	13	21	20	23	35	34	24
	Subtotal	**45**	**27**	**39**	**44**	**56**	**37**	**33**	**27**	**27**	**35**	**36**	**30**
24–59 months	**PCV7**	**25**	**6**	**5**	**1**	**3**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
	1	0	1	3	1	0	3	1	1	0	0	0	0
	3	2	1	3	3	5	2	2	2	1	3	4	1
	7F	1	3	2	2	4	2	3	1	1	0	0	0
	19A	4	8	5	20	18	22	16	6	2	4	3	1
	Other	11	3	13	14	15	8	13	12	10	14	13	6
	Subtotal	**43**	**22**	**31**	**41**	**45**	**38**	**35**	**22**	**14**	**21**	**20**	**8**
0–59 months	**PCV7**	**67**	**20**	**12**	**4**	**6**	**4**	**0**	**1**	**1**	**1**	**1**	**1**
	1	0	1	3	1	1	3	1	1	0	0	0	0
	3	5	4	5	6	8	4	4	6	2	3	4	3
	7F	3	9	10	7	20	6	7	2	1	1	0	0
	19A	12	19	28	58	61	56	32	18	9	7	5	6
	Other	27	23	51	45	41	28	44	38	44	69	59	37
	Total	**114**	**76**	**109**	**121**	**137**	**101**	**88**	**66**	**57**	**81**	**69**	**47**
	Rate /100,000	**30.6**	**20.2**	**28.3**	**30.3**	**33.1**	**23.6**	**20.1**	**14.9**	**12.8**	**18.1**	**15.5**	**10.6**

Source: LSPQ.

The epidemiology of serotype 3 is a special case. Between 2005 and 2010, the period during which no PCV contained the serotype 3 polysaccharide, 32 cases were observed, i.e. an average of 5.3 cases per year. Since 2015, the large majority of children under age five in Québec have been vaccinated with PCV13. In 2015–2016, there were 7 cases of serotype 3 reported, i.e. an average 3.5 cases per year, a reduction of less than 2 cases per year compared with the previous period.

A more detailed analysis was conducted on the IPD cases caused by vaccine serotypes in children under age five during the 2011–2015 period. The information was collected from several data sources as part of an epidemiological investigation ordered by the MSSS. The study period began with the introduction of PCV13 and information was obtained for all cases reported in children who received the PCV13 vaccine. However, the list of vaccine failures occurring with PCV7 and PCV10 before 2011 is incomplete and conclusions cannot be made in their regard. Research was performed on the clinical outcome and on the immunization status of children. The majority of the cases that occurred in children vaccinated with the PCV13 vaccine were caused by serotypes 19A and 3.

Of the seven IPD cases caused by serotype 3 among children vaccinated with PCV13 (Appendix 1), four occurred in immunocompetent children who had received three doses, as recommended, with a delay of more than one year between the booster shot and the first signs of the illness. This observation is consistent with the hypothesis of short-term protection conferred by PCV13 against serotype 3.

Serotype 19A caused, by far, the most vaccine failures, which occurred predominantly among vaccinated children with no immune deficiency (Appendix 2). Of the 27 cases reported among children vaccinated with PCV13, there were 17 in children between the ages of 8 and 14 months who had received the first two doses of the vaccine but had not yet received the booster dose, which suggests that there is a window of susceptibility in a 2+1 schedule. In 2014 and 2015, of the eight cases reported among children who had received at least one PCV13 dose, three occurred in children between the ages of 8 and 14 months (Appendix 2).

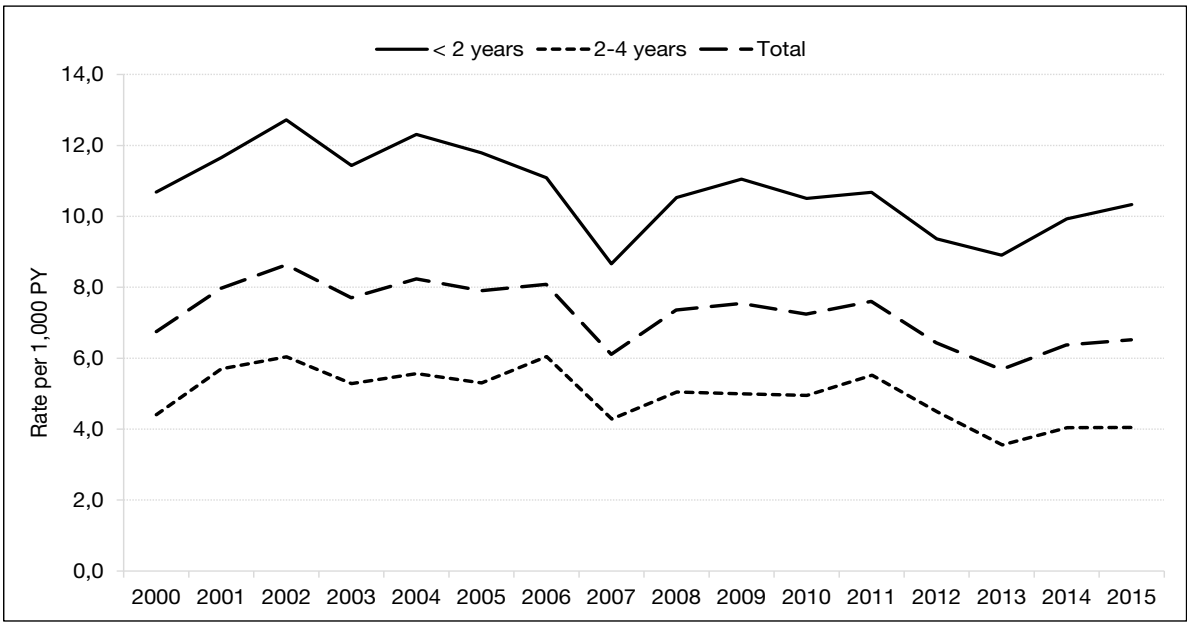
Among adults, there was minimal change in the overall incidence of IPD following the introduction of PCV7, and later PCV10 and PCV13 (8,9). In contrast, the distribution of serotypes changed considerably with a reduction in the proportion of cases caused by the serotypes present in PCV7 as early as 2005 and a replacement predominantly caused by serotypes 7F and 19A. Following the introduction of PCV10 in 2009 and PCV13 in 2011 for childhood immunizations, these two serotypes diminished and another replacement took place, this time due to a large number of serotypes not included in PCV13 (Figure 1). During this entire period, there was minimal change in the incidence of serotype 3 IPD among adults.

3.2 Pneumonia

In Québec, records in the hospital administrative Med-Écho database indicating a primary diagnosis of all-cause pneumonia are the only indicators available for monitoring pneumonia cases acquired in the community and leading to hospitalization. The frequency rates for the 2000–2015 administrative years are illustrated in Figure 2. A downward trend with fluctuations is observed for both the 0–2 and the 2–4 year old group. This downward trend could be partially due to the changes in the organization of pediatric hospital services and to hospitalization criteria. A detailed analysis of hospitalization rates for the various categories of lower respiratory infection in children under age five in Québec illustrated a reduced frequency of hospitalizations not requiring admission to intensive care that began before PCV7 was introduced in 2004. However, no change was identified in the frequency of all-cause hospitalizations requiring admission to intensive care (10). During the same

period, a shorter average hospitalization period was observed. Variations in the intensity of respiratory virus circulation could also explain the fluctuations observed. Pneumococcal vaccines may have helped reduce the frequency of pneumonia-related hospitalizations in the community, as suggested by a study in which changes in care practices and organization were controlled (11).

Figure 2 **Frequency (per 1,000 person-years) of hospitalizations with a primary diagnosis of pneumonia in children under age five in Québec, between 2000 and 2015**

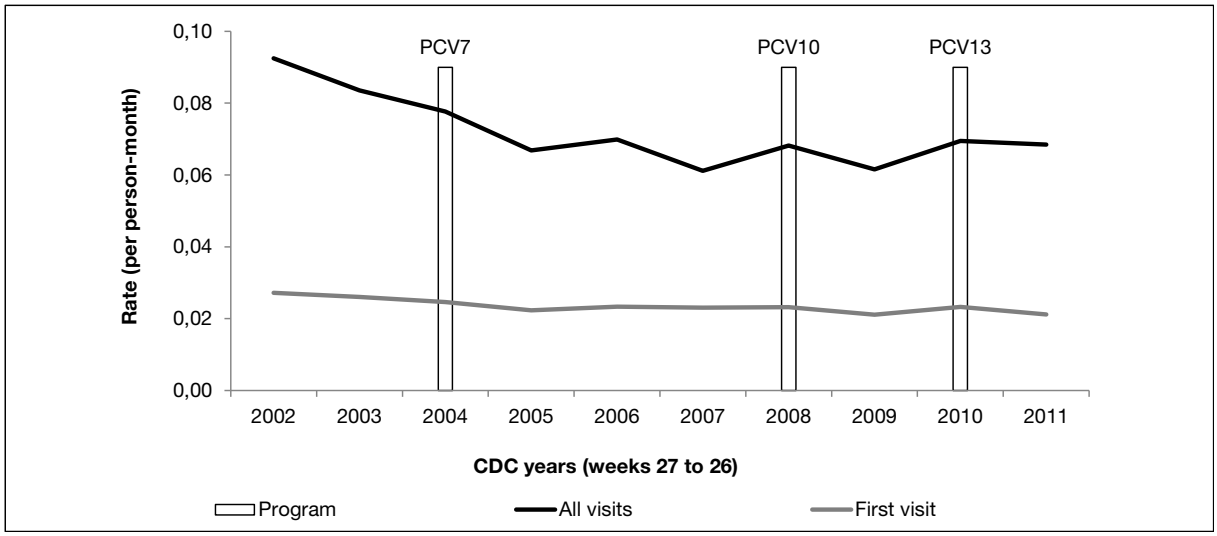


Source: Med-Écho database

3.3 Otitis

The only information available regarding otitis are the statistics from the file on medical services paid for by the RAMQ. These statistics cover all categories of otitis (ICD-9 codes: 381 and 382), including initial and follow-up visits. Figure 3 illustrates the frequency of medical visits among children under age two who are diagnosed with otitis. A reduced frequency is observed as of 2002, with a certain stabilization beginning in 2007. The reduction was much more substantial for all visits than for each child's initial visit. These trends may be partially explained by the modifications to practices involving the diagnosis of acute otitis media and the manner in which diagnoses are reported in reimbursement requests for medical treatment. Guidelines were issued to improve the specificity otitis diagnoses and to reduce, to a certain extent, antibiotic prescriptions (12–14). The resulting modifications of practices may have reduced the proportion of reimbursement requests for otitis diagnoses during the 2002–2007 period. Given this context, it is difficult to evaluate the impact of the introduction of PCV and impossible to confirm the superiority of a vaccination schedule.

Figure 3 Frequency of medical treatment reimbursement requests for children under age two in Québec who have been diagnosed with otitis (first and all visits)



Source: RAMQ file

4 Immunogenicity of vaccines

Predicting the clinical protection conferred by pneumococcal conjugate vaccines based on the results of immunogenicity studies is not a simple task. Various types of antibodies are produced and protection mechanisms are complex. The vaccine-induced serological response can be assessed using different methods at different times (15,16). The opsonophagocytic activity assay in vitro is a functional test that seems to be the best indicator in predicting protection against invasive disease (16). However, standardizing this test remains problematic. The notion that a common threshold of serum antibodies could be proposed to define the protection against the various serotypes has been discredited and it is now recognized that there are thresholds specific to each serotype (17). Moreover, the protection thresholds are different for invasive and mucosal infections, the latter requiring higher serum concentrations (18). Lastly, the very notion of threshold must be put into perspective and it would be more appropriate to talk about the probability of a disease occurring for the different serum antibody levels, measured shortly after the vaccine is administered (18).

PCV10 and PCV13 induce the development of antibodies to serotypes used in the composition of each vaccine, but also to the polysaccharides belonging to related serotypes, which can confer cross-protection. A review of studies directly comparing the immunogenicity of the two vaccines generally shows higher IgG geometric mean concentrations with PCV13 than with PCV10 for the 10 common antigens (2). However, the differences are substantially less for OPA titers and antibody avidity assays (19). PCV13 induces higher OPA titers than PCV10 for serotypes 6A, 19A and, of course, serotype 3 (19).

A non-randomized study assessed OPA titers in children who received 2+1 doses of PCV13 or two doses of PCV10, followed by one PCV13 booster (20). The only statistically significant differences in favour of the PCV13 2+1 schedule were related to serotypes 7F, 14 and 23F. For serotype 19A, there was a negligible difference in titers after the booster. For serotype 3, it seems that only one dose administered after the age of 12 months is as immunogenic as 2+1 doses. This last observation is corroborated by the results of another study comparing the PCV13 3+1 dose schedule with a schedule of two doses of PCV7 and one dose of PCV13 (21). A study comparing the various PCV13 immunization schedules demonstrated particularly low concentrations of serum antibodies to serotype 3 following a booster dose (22).

Pertussis vaccination in pregnancy is another aspect that must be taken into account when determining the immunogenicity of pneumococcal conjugate vaccines for newborns. The efficacy of a vaccine for pregnant women to prevent pertussis and its complications for newborns was recently demonstrated in studies conducted in the United Kingdom (23,24). Routine immunization of pregnant women, ideally in the beginning of the third trimester, is now recommended in certain countries, including Australia, the United States and the United Kingdom (23). In addition to the pertussis component, all the vaccines used contain tetanus and diphtheria toxoids. The diptheria toxoid is chemically related to CRM_{197}, the carrier protein used in PCV13. Hence, there is a potential for interference between the maternal antibodies present in the newborn of a mother vaccinated against pertussis when the child receives a vaccine at a young age that contains the diphtheria toxoid or CRM_{197}(25,26). A study conducted in the United Kingdom demonstrated that infants of mothers who were vaccinated with a DTaP-IPV vaccine had a lower serological response against pneumococcal disease when vaccinated with PCV13 at the age of two and four months (27). The same was shown in another study conducted in Belgium (28). The clinical meaning of such an interference is not known. To our knowledge, no other similar study has been conducted on children vaccinated with PCV10. However, most polysaccharide antigens in this vaccine are conjugated to the protein D of *Haemophilus influenzae* and only 19F is conjugated to the diphtheria toxoid. Therefore, the potential

for negative interference is theoretically lower. With a mixed schedule, after the age of one, no significant interference should normally occur with the first dose of PCV13, because the maternal antibodies against the diphtheria toxoid should have since disappeared by the age of 12 monrths.

In conclusion, it seems that there is little difference between PCV10 and PCV13 in terms of the immunologic response for common antigens. The advantage of PCV13 lies in the response against serotypes 19A and 3. The difference observed for serotype 6A is less important given that there is a high level of cross-protection against invasive disease caused by this serotype, conferred by antigen 6B, which is present in PCV10. This was demonstrated with the use of PCV7 (29). The advantage of a mixed schedule of two doses of PCV10 + one dose of PCV13 would be to increase protection against serotype 19A after the booster, and to thus prolong the duration of direct protection. An increase in the levels of antibodies to serotype 19A following the booster could have an effect on carriage and thus potentially maintain herd immunity. Regarding serotype 3, which PCV10 does not contain, a mixed schedule could have the same efficacy as a schedule that includes only PCV13, but only after the booster has been administered.

5 Efficacy against invasive disease

The results of studies that have been published or presented at conferences on the direct efficacy of PCV10 and PCV13 in preventing invasive disease in children are illustrated in Table 3. Two randomized trials were conducted on PCV10, but only case-control observational studies or those using the indirect cohort method (a variant of a case-control study) are available for PCV13. A quantitative synthesis is not feasible given the differences between the schedules, the definition of the vaccine status, age and the duration of follow-ups. In general, both vaccines are very effective in preventing invasive disease caused by the serotypes contained in the respective vaccines.

An ecological study conducted in Finland following the introduction of PCV10 strongly suggests that this vaccine provides cross-protection against serotype 6A IPD (30). Note that PCV7, which, like PCV10, contains the 6B polysaccharide, confers a high level of cross-protection against IPD caused by serotype 6A(29).

There is evidence of the efficacy of PCV10 in preventing the IPD caused by serotype 19A; the short-term estimates are not much different from those obtained with PCV13 (Table 3). Given that the antibody levels induced by PCV10 are lower than those generated by PCV13 against 19A(2), the cross-protection may not last as long as direct protection. This matter has been raised in Finland (Palmu, personal communication). This problem could be resolved with the use of a mixed schedule, since the antibody titers obtained following the booster are close to those observed after the booster in a 2+1 PCV13 schedule (20).

PCV10 does not cover serotype 3 and protection cannot be expected from a 2+1 PCV10 schedule. For PCV13, protection estimates against serotype 3 are systematically lower than for other vaccine serotypes (Table 3). This lesser efficacy seems to be particularly true for the 2+1 schedule, as demonstrated in the United Kingdom (17). No data exists on the protection conferred against serotype 3 IPD with a single dose of PCV13 at 12 months of age.

The Swedish study on the epidemiology of IPD is especially interesting, because some counties switched from PCV7 (introduced in 2008–2009) to PCV10 beginning in 2010, and another from PCV7 to PCV13 (31). Overall, a reduction in IPD caused by vaccine serotypes has been observed in all age groups, as well as a variable increase of non-vaccine serotypes. The overall incidence of IPD has decreased in children following the introduction of PCV7 and new-generation vaccines. Similar decreases were observed in PCV10 and PCV13 counties. In adults, the overall incidence of IPD has not changed significantly in either group. Serotype 19A increased in counties using PCV10, and decreased those using PCV13. On the other hand, there was a more substantial increase in non-vaccine serotypes in PCV13 counties compared with PCV10 counties, which explains why there was no significant difference in the incidence of all serotype IPD.

The case-control study initiated in Québec in 2005 (32) was pursued and the preliminary results, which include cases reported up to December 31, 2016, are now available (Table 4). In general, the efficacy estimates are slightly lower than those determined in the study that ended in 2013. PCV10 ≥ 1 dose against the 13 serotypes = 78% efficacy compared with the previous 84% and PCV13 ≥ 1 dose against the 13 serotypes = 82% efficacy compared with the previous 86% (33). This could be the result of the longer follow-up period and of a possible reduction in protection due to the time elapsed since the last dose. The other observation is the absence of a major difference between the various vaccines and schedules. The cross-protection efficacy provided by PCV10 against serotype 19A is not much different from the direct protection conferred by PCV13, although the latter may provide a slight advantage after three doses. For serotype 3, there are few cases and estimates have very wide confidence intervals. PCV13 confers no significant protection against serotype 3.

In conclusion, the data from Sweden and Québec are reassuring in terms of the relative performance of the different schedules in preventing invasive disease in children.

Table 3 Results of studies on the direct efficacy of pneumococcal conjugate vaccines against invasive disease in children

References	PCV	Type of study and context	Background	Analysis	IPD serotypes				
					PCV10	6A	19A	3	PCV13
Trenaghi et al., 2014(34)	10	RCT in three Latin American countries	No prior PCV7 use; 3+1 doses per protocol	Per protocol ≥ 1 dose	100% (74 to 100)	-99% (-2,090 to 82)		ND	ND
Palmu et al., 2013(35)	10	Randomized trial on communities in Finland	No prior PCV7 use; 3+1 or 2+1 doses per protocol	Per protocol ≥ 1 dose	100% (91 to 100)	ND	ND	ND	ND
Domingues et al., 2014(36)	10	Matched case-control study in Brazil	No prior PCV7 use; 3+1 doses recommended	Age-appropriate vaccination ≥ 1 dose	84% (66 to 92)	15% (-312 to 82)	82% (11 to 96)	6% (-278 to 76)	ND
Verani et al., 2015(37)	10	Indirect cohort in Brazil	No prior PCV7 use; 3+1 doses recommended	All ages ≥ 1 dose	73% (44 to 87)	51% (-52 to 84)	71% (17 to 90)	ND	ND
Deceuninck et al., 2015(33)	10	Unmatched case-control study in Québec	Prior PCV7 use; 2+1 doses recommended	All ages ≥ 1 dose	97% (84 to 99)		71% (24 to 89)	ND	84% (65 to 93)
Moore et al., 2015(38)	13	Matched case-control study in the United States	Prior PCV7 use; 3+1 doses recommended	All ages ≥ 1 dose	ND	ND	86% (76 to 94)	80% (20 to 94)	86% (76 to 92)
Andrews et al., 2014(17)	13	Indirect cohort in the UK	Prior PCV7 use; 2+1 doses recommended	≥ 1 dose < 1 year of age or 1 dose ≥ 1 year of age	ND	98% (64 to 100)	67% (33 to 84)	26% (-69 to 68)	75% (58 to 84)

ND: Not determined.

Table 3 Results of studies on the direct efficacy of pneumococcal conjugate vaccines against invasive disease in children (continued)

References	PCV	Type of study and context	Background	Analysis	IPD serotypes				
					PCV10	6A	19A	3	PCV13
Deceuninck et al., 2015(33)	13	Unmatched case-control study in Québec	Prior PCV7 use; 2+1 doses recommended	All ages ≥ 1 dose	N/A	N/A	74% (11 to 92)	ND	86% (62 to 95)
Guevara et al., 2016(39)	13	Matched case-control study in Spain	Prior PCV7 use; 3+1 doses recommended	All ages ≥ 1 dose	ND	ND	ND	ND	96% (43 to 100)
Van der Linden et al., 2016(40)	13	Indirect cohort in Germany	Prior PCV7 use, 3+1 doses recommended	≥ 1 dose < 2 years	ND	90% (56 to 100)	77% (47 to 90)	74% (2 to 93)	86% (74 to 93)
Weinberger et al., 2016(41)	13	Indirect cohort in Germany	Prior PCV7 use; 3+1 doses recommended	≥ 2 doses < 12 months or ≥ 1 dose ≥ 12 months	ND	ND	83% (41 to 95)	0% (-791 to 89)	85% (64 to 94)
Su et al., 2016(42)	13	Matched case-control study in Taiwan	Prior PCV7 use; 3+1 doses recommended	All ages ≥ 1 dose	ND	ND	82% (63 to 91)	ND	ND
Cohen et al., 2017(2)	13	Matched case-control study in South Africa	Prior PCV7 use; 3+1 doses recommended (6 and 14 weeks, 9 months)	All ages ≥ 2 doses	ND	ND	ND	ND	85% (37 to 91)
Savulescu et al., 2014(43)	13	Indirect cohort in 10 sites in Europe	Prior PCV7 use; 3+1 or 2+1 doses recommended	2 months–4 years ≥ 1 dose	ND	ND	86% (74 to 92)	70% (44 to 84)	87% (80 to 91)
				1–4 years 3 or 4 doses	ND	ND	94% (82 to 98)	57% (5 to 81)	86% (76 to 92)

ND: Not determined

Table 4 Efficacy[1] of various schedules (VE) against invasive pneumococcal disease (IPD) in children under age five in Québec: Control-case analysis of cases occurring between 2000 to 2015, based on the vaccine schedule

Number of doses		Vaccine		
		PCV10	PCV13	PCV10 + 13
Invasive disease caused by serotypes included in PCV13				
≥ 1 dose	No. vaccinated cases	21	34	N/A
	Efficacy	78%	82%	
	95% CI	55% to 89%	62% to 91%	
= 2 doses	No. vaccinated cases	11	18	0
	Efficacy	74%	76%	100%
	95% CI	36% to 89%	46% to 89%	ND
= 3 doses	No. vaccinated cases	6	12	5**
	Efficacy	81%	87%	78%
	95% CI	48% to 93%	67% to 94%	34% to 92%
≥ 3 doses	No. vaccinated cases	6	13	5**
	Efficacy	82%	87%	83%
	95% CI	51% to 94%	68% to 94%	51% to 94%
Invasive disease caused by serotype 3				
≥ 1 dose	No. vaccinated cases	2	9	N/A
	Efficacy	-36%	-32%	
	95% CI	-1,225% to 86%	-1,220% to 87%	
= 2 doses	No. vaccinated cases	1	1	0
	Efficacy	-41%	71%	100%
	95% CI	-2,242% to 91%	-485% to 99%	ND
= 3 doses	No. vaccinated cases	0	6	1**
	Efficacy	100%	-54%	-33%
	95% CI	ND	-1,651% to 86%	-2,110% to 92%
= 3 doses	No. vaccinated cases	0	7	1***
	Efficacy	ND	-56%	10%
	95% CI		-1,626% to 86%	-1,367% to 95%
Invasive disease caused by serotype 19A				
≥ 1 dose	No. vaccinated cases	16	24	N/A
	Efficacy	52%	61%	
	95% CI	-21% to 81%	-10% to 86%	
= 2 doses	No. vaccinated cases	9	16	0
	Efficacy	42%	33%	100%
	95% CI	-74% to 81%	-101% to 77%	ND

[1] Efficacy rate adjusted according to the year, age, season and existence of a risk factor for invasive pneumococcal disease.

Table 4 Efficacy of various schedules (VE) against invasive pneumococcal disease (IPD) in children under age five in Québec: Control-case analysis of cases between 2000 and 2015, based on the vaccine schedule (continued)

Number of doses		Vaccine		
		PCV10	PCV13	PCV10 + 13
= 3 doses	No. vaccinated cases	5	6	4**
	Efficacy	60%	83%	58%
	95% CI	-36% to 88%	37% to 95%	-57% to 89%
≥ 3 doses	No. vaccinated cases	5	6	4***
	Efficacy	63%	85%	69%
	95% CI	-26% to 89%	45% to 96%	-16% to 92%

Source: Unpublished data.

N/A = Not applicable; ND = Not determined; ** PCV10 + PCV10 + PC13 schedule; *** All combinations ≥ 3 doses PCV10 – PCV13.

6 Efficacy against non-invasive pneumonia

It is difficult to accurately measure the efficacy of PCV10 and PCV13 in preventing non-invasive pneumococcal pneumonia. In children, there is no test or combination of tests that can diagnose, with sensitivity and specificity, a non-invasive (or non-bacteremic) pneumococcal pneumonia, let alone determine the serotype involved. For this reason, clinical and radiological criteria are generally used, possibly in combination with biochemical tests (34). The results of a randomized clinical trial provide information on the direct protection conferred by a vaccine, but not on the indirect effects associated with herd immunity and the phenomenon of replacing vaccine serotypes with non-vaccine serotypes. The use of administrative databases in before-after-control-impact (BACI) or time-series designs is problematic given the uncertain validity of the codes used to record hospitalizations and medical procedures, as well as the temporal variations that can occur in the accessibility and organization of health services, the use of diagnostic tests, hospitalization criteria, and coding practices. In adults, there are differences between the distribution of serotypes identified in invasive pneumococcal disease and in non-invasive pneumonia, with a greater diversity of serotypes in the latter category, as observed in Ontario (44). We can reasonably assume that the same differences would be seen in children.

In a randomized trial conducted in South America, PCV10 was shown to have an efficacy of 22.4% (95% CI: 5.7% to 36.1%) in preventing pneumonia with a radiologic image of consolidation and 7.3% (95% CI: 1.6% to 12.6%) for all cases of pneumonia diagnosed based on clinical criteria (34). In a group-randomized trial conducted in Finland, the efficacy of PCV10 was 28.3% (95% CI: 4.0% to 46.0%) for cases of pneumonia confirmed by radiograph, including those with and without an image of consolidation(45). In the latter study, there was no statistically significant difference between the groups of children who received three (2+1) or four (3+1) doses of vaccine. PCV13 was approved based on immunological criteria compared to PCV7, and there are no clinical outcome results from randomized trials. In a randomized trial in California, PCV7 was shown to have an efficacy of 4.3% (95% CI: -3.5% to 11.5%) in preventing the initial episodes of clinically diagnosed pneumonia and 20.5% (95% CI: 4.4% to 34.0%) in preventing episodes with radiological confirmation (46). In a randomized trial involving adults in the Netherlands, the efficacy of PCV13 was 75.0% (95% CI: 41.4% to 90.8%) for invasive disease caused by vaccine serotypes and 45.0% (95% CI: 14.2% to 65.3%) for non-invasive pneumonia caused by vaccine serotypes (47). We can assume that the same ratio of efficacy rates (45%/75% = 0.6) would be found in children.

In a recent systematic review, 32 studies on PCV10 or PCV13 using case-control and BACI designs were analyzed (2). The vaccine efficacy results were highly heterogeneous, with effects varying from -13% to -68% in terms of the frequency of clinically diagnosed pneumonia, and between -34% and -66% for pneumonia with radiological confirmation. The authors concluded that there was no evidence of one vaccine being better than another in preventing pneumonia. No study in this review involved a direct comparison of the two vaccines.

An analysis of all-cause pneumonia hospitalization rates was done in Sweden, where PCV7 was introduced in 2008–2009, and then replaced with PCV10 or PCV13 starting in 2010, with the choice of vaccine being made by each county (48). The results of this time-series study are difficult to interpret, as the two groups of counties are not socioeconomically and demographically comparable, the new vaccines were introduced gradually and on different dates, and the history of each county is not given. In addition, the statistical analyses presented are not appropriate and do not take into account, among other things, the heterogeneity of trends between counties.

In Québec, cohorts of children were exposed to different vaccination schedules, including PCV10 alone, PCV13 alone, and a combination of the two vaccines, most often two doses of PCV10 in the first year and a booster dose of PCV13 after the age of 12 months. The Med-Écho database is currently being analyzed for hospitalizations with a main diagnosis of all-cause pneumonia. Preliminary results indicated that the risk of pneumonia was lowest in the cohorts of children exposed to PCV13 (49). However, the results are difficult to interpret given the changes over the years to the organization of services, including the creation of pediatric observation units, the introduction of new antibiotics that facilitate outpatient treatment, and the general trend toward reducing the number of hospital stays. At this stage, it is impossible to state whether one vaccination schedule is better than another at preventing all-cause pneumonia hospitalizations in children.

7 Efficacy against otitis

The efficacy of PCV10 in preventing acute otitis media (AOM) was demonstrated in a randomized trial (34). After a 30-month follow-up period, the protection rate was 16.1% (95% CI: -1.1% to 30.4%) for clinically diagnosed AOM and 67.1% (95% CI: 17.0% to 86.9%) for AOM confirmed by culture and caused by pneumococcal disease belonging to the vaccine serotypes. In a subsample of children who participated in the group-randomized trial in Finland, the estimated protection against all episodes of otitis was 6.1% (95% CI: -2.7% to 14.1%) in the 3+1 PCV10 group and 7.4% (95% CI: -2.8 % to 16.6 %) in the 2+1 PCV10 group (50). An effect of PCV10 was also observed on prescriptions of antibiotics indicated for the treatment of AOM: -8% (95% CI: -1% to -14%) in the PCV10 groups combined, compared to the control group (35). However, these data do not allow us to fully determine the potential impact of a program given herd immunity and the replacement of the vaccine serotypes with other serotypes.

As for PCV13, we only have results from ecological studies in populations that are not very representative and that mainly include cases of complicated or treatment-resistant otitis. In an Israeli study, a 77% decrease in cases of otitis with positive pneumococcal cultures was noted between 2004 and 2013, during which time PCV7 and then PCV13 was used in the national immunization program (51).

A time-series analysis conducted in Sweden on administrative records indicates that the introduction of PCVs was followed by a decrease in the frequency of medical visits for otitis, myringotomy, and ventilation tube insertions; the decrease was more marked in counties that used PCV10 than in those that opted for PCV13 (52). However, these results must be interpreted with caution, given the geographic variations that existed in the rates observed prior to the use of PCV7 and possible temporal changes in the behaviour of parents and doctors in suspected cases of AOM.

The analysis done in Québec based on billings for medical visits with a diagnosis of otitis does not allow us to draw robust conclusions on the differences between the different schedules that include PCV10 or PCV13.

8 Indirect effects

8.1 Effect on carriage

To induce herd immunity, a pneumococcal conjugate vaccine must have an effect on the nasopharyngeal carriage of *Streptococcus pneumoniae*. Knowing that the pneumococcal carriage rate is highest in children aged 2–3 years, the antibodies generated by a booster dose after the age of 12 months will be the most decisive in inducing herd immunity (53). The indirect effect of an immunization program with a pneumococcal conjugate vaccine is quick to appear. However, it takes several years to achieve a balance between the slowdown in the transmission of vaccine strains in the general population and the replacement of vaccine serotypes with non-vaccine serotypes (54).

A systematic review of the effect on the asymptomatic carriage of PCV10 (14 studies) and of PCV-13 (15 studies) shows a reduction in the prevalence of vaccine serotypes that appears quickly and then evolves (2). The speed and scope of the effects appear to be influenced by the distribution of serotypes at the start, the vaccine coverage, the existence or not of a catch-up program, and the schedule itself (booster or no booster). The same effect was also observed following a transition from PCV7 to PCV13, whereas there are no studies on the transition from PCV7 to PCV10 other than in Québec. This review did not include a study with satisfactory power in which the effect of PCV10 was compared directly to PCV13, nor a study on a mixed PCV10 + PCV13 schedule.

When examining the effect for each serotype, we observe a modest effect of PCV10 on serotype 6A (10–20% reduction in carriage) and the absence of effect on serotype 3 (2). In a randomized trial, PCV10 had a null effect on the carriage of strains of serotype 19A, and variable results (no effect, increase or decrease) were reported in observational studies (55). The results on the effect of PCV10 on the carriage of nontypeable *Haemophilus influenzae* strains are unconvincing (56). There is no observed effect of PCV13 on serotype 3, although the data are imprecise (2). However, this vaccine has a significant effect on the carriage of serotypes 6A and 19A (2,55).

In general, the effect of a PCV resulting in a decrease in the prevalence of vaccine serotypes appears to be entirely offset by an increase in the prevalence of non-vaccine serotypes, without affecting the overall prevalence of pneumococcal carriage (57).

Based on these observations, we can predict that PCV10 could have an indirect effect on invasive disease caused by the vaccine serotypes, but not necessarily serotype 19A. We can also predict that PCV13 would have an indirect effect on all vaccine serotypes, except for serotype 3. However, the overall effect of these two vaccines on all cases of invasive disease is difficult to predict given the highly variable nature of serotype replacement (54).

8.2 Effect on invasive disease

The *de novo* introduction of PCV10 or PCV13 in an immunization program or a transition from PCV7 to PCV10 or PCV13 resulted in a decrease in the incidence of the vaccine serotypes in adults and an increase in the incidence of the non-vaccine serotypes (2). The magnitude of the herd immunity and serotype replacement phenomena varies, and, as such, the overall incidence of IPD in adults may either decrease substancially, as seen in the United States (38), decrease less as seen in the United Kingdom, Norway and the Netherlands (58–60), or remain unchanged, as in Québec and Ontario (61). The use of PCV10 generally leads to an increase in the incidence of 19A in adults, but also to a lesser increase in the serotypes not covered by PCV13 compared to the situation when PCV13 is used (2). There are no ecological studies that have specifically assessed the indirect effects of a mixed PCV10 + PCV13 schedule, but it can be assumed, based on the immunogenicity data, that the overall impact will be situated between that observed with PCV10 alone and with PCV13 alone. As in Québec, the overall incidence of IPD in adults has not changed substantially since the introduction of PCV7, PCV10 and PCV13, so we can reasonably predict that a return to a 2+1 PCV10 or mixed (2 PCV10 + 1 PCV13) schedule will have no perceptible impact (9) on the overall IPD rate in adults.

8.3 Effect on non-invasive disease

The incidence of all-cause pneumonia in adults is the best indicator of the indirect effect of using pneumococcal conjugate vaccines in children and of the latter's contribution to public health. This is generally done as part of a before-after comparison or time-series design. Most studies of this nature were based on hospital statistics (2). These types of studies are difficult to interpret because the expected effect is modest in a serotype replacement situation, and because there is an increased proportion of people with comorbidities in the elderly population, as well as significant variations in the incidence of viral infections, including influenza. Consideration must also be given to temporal variations in access to and organization of health services, in the eligibility criteria for an acute care unit, and in coding practices. In a study conducted based on hospital statistics from several countries, including the United States, no indirect impact of introducing PCVs was detected in adults when the statistics were adjusted for all of the confounding factors mentioned (11).

9 Vaccine safety

Since the first pneumococcal conjugate vaccine was approved in 2000, hundreds of millions of doses of PCV7, PCV10 and PCV13 have been administered without any major safety issues (62). The results of numerous clinical trials with PCV10 or PCV13 have shown only episodes of fever and generally minor pain at the injection site (63–69). In a clinical trial in the United Kingdom, children already immunized with PCV13 received a booster dose of PCV10 or PCV13 at the age of 12 months (70). Pain at the injection site was scored slightly higher with PCV13 than with PCV10 (7.7 vs.7.2; $p = 0.04$), with a tendency toward longer crying time. In Québec, the analysis of side effects reported based on the periods of use of the different vaccines revealed a higher frequency of reported side effects with PCV7 and PCV13 than with PCV10, without the emergence of a particular clinical entity (MSSS, written communication). While there are benefits to using a less reactogenic vaccine, especially in very young children, reactogenicity is not a major decision-making criteria.

10 Economic considerations

Approximately 240,000 doses of PCV13 are administered annually in Québec (86,000 births x 93% coverage x 3 doses on average), at a substantial cost. If a request for proposals were to be issued to two pharmaceutical companies, a pneumococcal conjugate vaccine could likely be obtained at a lower price. This is precisely what happened with PCV10 in Finland, the Netherlands, and Belgium (Arto Palmu, Lieke Sanders and Germaine Hanquet, personal communications). However, negotiations with two companies would be more complicated in the case of a mixed schedule.

Each dollar saved on the unit cost of the vaccine would represent annual savings of $240,000 in Québec. Assuming a $10 decrease in the price per dose of PCV10, this would correspond to $2.4 million in savings, and $4.8 million in savings if the price per dose were to decrease by $20. In the case of a mixed schedule, the savings would be $1.6 million and $3.2 million for a price drop of $10 and $20, respectively, provided the price of PCV13 remained stable.

From a public health standpoint, it is difficult to estimate the possible differences in adopting a 2+1 PCV10 or 2 PCV10 + 1 PCV13 schedule, compared to the current 2+1 PCV13 schedule. Throughout Québec, there are children who have been immunized according to all sorts of schedules made up of the three vaccines. As such, it is impossible to determine the effect of one particular schedule on the transmission dynamics of pneumococcal disease in the general population. A new equilibrium between herd immunity and serotype replacement does not yet seem to have been reached since PCV13 was first introduced in 2011 (9).

Experience has shown that the overall incidence of IPD in adults did not change following the successive introduction of the three conjugate vaccines in the pediatric immunization program (Figure 1). Therefore, it is likely that another change would have only minimal effect on the overall incidence of IPD, even if the distribution of the serotypes causing the disease were to differ depending on the schedule used. As such, we would likely see a larger proportion of cases caused by serotype 19A in a 2+1 PCV10 scenario, although with a smaller proportion of non-vaccine serotypes, as was the case in Sweden (31). This could influence the choice of vaccines and the vaccine schedule in adults. The increase in the proportion of IPD caused by serotype 19A in adults could support the introduction of PCV13 in addition to PPSV23 in the immunization program for seniors.

Since there is no conclusive evidence that one schedule is better than another in preventing all-cause pneumonia and otitis in children (2), the decision will have to be based on forecasts of invasive disease in children. The various schedules would differ essentially in the incidence of disease caused by strains of serotypes 3 and 19A. The data available in Québec indicate that we could expect a difference of two cases per year of serotype 3 between the 2+1 PCV10 schedule and the 2+1 PCV13 schedule. With a mixed schedule, we could expect a difference of one case per year on average, knowing that protective antibodies are generated by a single dose of PCV13 after the booster dose at age one (20). The assumptions about the differences between the various schedules are more tenuous with respect to serotype 19A. PCV10 seems to provide direct cross-protection against this serotype. However, it is less clear whether it can provide herd immunity. This possible absence of herd immunity would not help in reducing the risk of disease in infants who are still not vaccinated and in the small proportion of older children who are unvaccinated or not yet fully vaccinated. For its part, the mixed schedule could provide direct and indirect protection very similar to that offered by a 2+1 PCV13 schedule and higher protection than that provided by a 2+1 PCV10 schedule.

A possible scenario for a 2+1 PCV10 schedule would involve an increase of two cases per year of serotype 3 compared to the current situation in children under age five and, possibly, a doubling of the number of cases of serotype 19A, to the level seen in 2005, at the very beginning of the universal vaccination program. Compared to current numbers, there would be a total of eight additional cases per year, with no change in the incidence of serotypes other than 3 and 19A. We assumed that the difference would be half as high with a mixed schedule. However, it is possible that all these differences could be minimal or nil, as was seen in Sweden (31). We also conducted sensitivity analyses to determine what the minimum number of additional cases compared to the current situation would need to be in order to generate an incremental cost-effectiveness ratio of $45,000/QALY,[2] which is the gross domestic product (GDP) per capita in Canada and one of the thresholds that defines a desirable intervention (71). Another threshold is a value three times the GDP, i.e. $135,000/QALY, which would be considered an acceptable indicator of cost-effectiveness (71).

We made the assumption that the proportion of serious disease, including meningitis and empyema, was 47% for serotype 3 and 14% for serotype 19A, with proportions of 5% and 2%, respectively, for meningitis, as was seen in Québec (appendices 1 and 2). For deaths due to IPD, we used the rate of 4.8% observed in the United Kingdom in children aged five and under (72). As for meningitis, we assumed that one-third of survivors would have neurological sequelae (73). Another assumption concerns the frequency of severe neurological sequelae post-meningitis, established at 19%, and that of isolated deafness, at 26% of all patients (6). The utility value was set at 0.6 for neurological sequelae and at 0.8 for deafness (74). Life expectancy post-IPD at a young age is 80 years, which corresponds to 30 years at an annual discount rate of 3%. Based on these assumptions, we can estimate the number of QALYs lost in the scenarios where PCV10 or a mixed schedule is used instead of PCV13 (Table 5).

The cost-effectiveness indices generated by a 2+1 PCV10 schedule, which would result in an increase of eight cases per year, are presented in Table 5. The results are interpreted as follows: With a PCV10 price under $10 per dose compared to PCV13, keeping the current schedule would not be economically beneficial, with a cost per QALY gained of $190,000 for the most effective schedule. At a price difference of $20 per dose, this index would jump to $351,000/QALY. The economic acceptability thresholds are also exceeded with a 2+1 PCV13 schedule compared to the mixed schedule, with incremental costs being $254,000/QALY and $507,000/QALY, respectively. If we compare the mixed schedule to the 2+1 PCV10 schedule (right-hand column in Table 5), we can see that the 2+1 PCV-10 schedule generates better incremental cost-effectiveness ratios (ICER) than the mixed schedule, but that the latter option would be acceptable with a $10 per dose price difference between the two vaccines in the chosen scenario (ICER = $127,000/QALY).

To achieve a threshold of $45,000/QALY with a $10 per dose price difference between the two vaccines, the 2+1 PCV10 schedule would have to result in 34 additional cases of IPD per year compared to the current number of cases reported in children under age five (47 cases), i.e. a 72% increase (81 cases vs. 47 cases). At a $20 per dose price difference, there would have to be 68 additional cases in order to reach the threshold, i.e. a 144% increase in the incidence rate. With the mixed schedule and a $10 per dose price difference between the vaccines, the annual number of cases would have to increase by 45 compared to the current situation in order to reach the threshold at which the 2+1 PCV13 schedule would be considered the most economically sound.

[2] QALY: quality-adjusted life year.

Therefore, the economic analyses show that in plausible scenarios involving a small increase in the number of cases over the current situation, the 2+1 PCV10 and mixed schedules are more advantageous. The number of cases would have to increase substantially in order to affect this conclusion, which is unlikely. If, as observed in Sweden (31), we assume that the 2+1 PCV10 and 2+1 PCV13 schedules will be equivalent for IPD, then we need to choose the schedule that uses only the least expensive vaccine. We did not conduct sensitivity analyses of the differential efficacy rates of the various schedules for pneumonia and otitis. Given the major financial burden of otitis compared to invasive disease and pneumonia (74), a vaccine that would reduce the incidence of otitis would have a strong economic advantage.

Table 5 Benefits and annual marginal costs of schedules using PCV10 compared to the schedule that exclusively uses PCV13 in children under age five in Québec, in a scenario of unfavourable vaccine efficacy with PCV10

Schedule	**2+1 PCV10**	**2 PCV10 + 1 PCV13**	
	(a)	(b)	(a) vs. (b)
Additional cases	8	4	4
Severe cases (21%)	1.68	0.84	0.84
Death (4.8%)	0.4	0.2	0.2
Meningitis (2%)	0.16	0.08	0.08
Sequelae (31.7% of meningitis cases)	0.05	0.03	0.03
Quality-adjusted life years (QALY) lost	12.61	6.31	6.31
Marginal cost ($10/dose)	$2,400,000	$1,600,000	$800,000
Cost/case avoided	$300,000	$400,000	$200,000
Cost/QALY	$190,259	$253,678	$126,839
Marginal cost ($20/dose)	$4,800,000	$3,200,000	$1,600,000
Cost/case avoided	$600,000	$800,000	$400,000
Cost/QALY	$380,518	$507,357	$253,678

* Assuming 26% of meningitis patients will experience neurological sequelae at a utilitarian value of 0.6, that 19% of survivors will experience deafness at a utilitarian value of 0.8, that the life expectancy of survivors is 80 years, corresponding to 30 years at an annual discount rate of 3%. The costs per case avoided and per quality-adjusted life year (QALY) gained correspond to the investment that would be needed to maintain the health benefits provided by the more effective, more expensive schedule compared to the less effective, but also less expensive schedule.

11 Other considerations

11.1 Feasibility

If a mixed schedule were chosen, it would not be the first time in Québec that different vaccines were administered at different ages. However, using two vaccines in a mixed schedule could cause some problems in the field by complicating the inventory management process. Administration errors could also occur. Administering PCV13 instead of PCV10 would be inconsequential. Administering PCV10 instead of PCV13 for the 12-month booster dose would be of practically no consequence given the low circulation of serotypes 3 and 19A, and the negligible difference in efficacy between the two vaccines. These types of errors could be minimized by giving immunization providers sufficient information.

11.2 Compliance

PCV10 and PCV13 are used widely around the world. In Europe, for example, PCV13 is used in France, the United Kingdom and Italy. However, some countries, such as the Netherlands, Belgium, Finland and Iceland, opted for PCV10 further to a request for proposals. In other countries like Sweden, Germany, Slovakia, and the Czech Republic, both vaccines are used. The Netherlands transitioned from PCV7 to PCV10, and Belgium from PCV13 to PCV10. To date, there has been no cause to question these choices. At the moment, no country uses a mixed schedule.

11.3 Acceptability

Certain clinicians and experts tend to prefer PCV13 to PCV10 (12), probably due to the belief that a greater number of antigens is always preferable and that cross-protection is tenuous. A mixed schedule including a booster dose of PCV13 could be seen as reassuring to people who are convinced that PCV13 is superior to PCV10. In a recent review commissioned by the World Health Organization, the authors do not state that one of the two vaccines is better or worse than the other and recommend that the choice be based on a range of considerations, including product availability, the epidemiological context, the potential efficacy of the two vaccines, and economic factors (2). Whatever decision it makes, the MSSS will have to clearly explain its reasoning to the population and to healthcare professionals in particular.

12 Conclusions

The main decision-making elements are listed in Table 6.

First finding: The three schedules analyzed are all defensible and none can be rejected outright. Many industrialized countries use 2+1 PCV10 and 2+1 PCV13 schedules, and a mixed schedule must not be inferior to a 2+1 PCV10 schedule.

Second finding: When it comes to making a decision, the two greatest uncertainties are the number of additional cases of IPD that could occur in children with a 2+1 PCV10 or mixed schedule compared to the current PCV13 schedule, as well as the price difference between the two vaccines. The cost-effectiveness ratios of the various scenarios will be adjusted by the combination of these two parameters.

If the objective is to preserve health gains regardless of the cost and cost-effectiveness of the program, then the safest option would be to keep the current 2+1 PCV13 schedule. Keeping the current schedule would also be preferable if the difference between the costs of PCV10 and PCV13 were low. If we think there will be little or no difference in the number of IPD cases, then the 2+1 PCV10 schedule is the most effective option, assuming a unit price less than that of PCV13.

The active members of the CIQ unanimously voted in favour of a mixed schedule rather than a PCV13-only schedule, provided the price difference is significant. A mixed schedule seems safe enough to preserve the gains made by the current PCV13 schedule in terms of reducing the burden of the disease in children and preventing the risk of an increased incidence of 19A in the general population. Moreover, in most scenarios, the mixed schedule has an economic advantage over the current 2+1 PCV13 schedule.

Given the uncertainties surrounding the price and purchasing conditions of the vaccines, it would be wise not to issue an unequivocal recommendation and to allow the Ministère de la Santé et des Services sociaux to make the final decision based on its priorities and the proposed prices. Should it be impossible to negotiate the purchase of vaccines for a mixed schedule and should the only option be to choose between keeping the current 2+1 PCV13 schedule or opting for a 2+1 PCV10 schedule, then a new consultation would be needed.

Whatever the final decision, active and ongoing surveillance of the epidemiology of IPD and pneumonia-related hospitalizations needs to continue. Should the disease epidemiology change, the CIQ's scientific advisory will be reviewed and the program adjusted accordingly.

A supplementary scientific advisory regarding the recommended schedule for high-risk groups, including children living in Québec's northern regions, will be written at a later time.

Table 6 Summary of the advantages and disadvantages of the different childhood vaccination schedules to prevent pneumococcal disease in Québec

Decision-making factor	2+1 PCV13	2+1 PCV10	Mixed schedule
Immunogenicity	Possibility of negative interaction during the 2- and 4-month doses in the event of vaccination of pregnant women against pertussis.	Functional antibody titre (OPA) lower for serotypes 6A and 19A, and absence of response against serotype 3.	Functional antibody titre (OPA) lower for serotypes 6A and 19A, and absence of response against serotype 3 before booster dose.
Direct protection against IPD	High protection against 12 of the 13 serotypes included in the vaccine, but low protection against serotype 3. These advantages are partially eroded by serotype replacement.	High protection against the serotypes included in the vaccine and against 6A and 19A, but absence of protection against serotype 3. These advantages are partially eroded by serotype replacement.	Following the booster dose: higher protection against 12 of the 13 serotypes included in PCV13 with reinforcement of protection against serotype 19A and possible modest protection against serotype 3—only after the booster dose. These advantages are partially eroded by serotype replacement.
Protection against pneumonia	Probable modest protection against 12 of the 13 serotypes included in the vaccine and uncertain protection against serotype 3. A good part of these advantages are likely eroded by serotype replacement.	Probable modest protection against the 10 serotypes included in the vaccine, possibly against serotypes 6A and 19A, and absence of protection against serotype 3. A good part of these advantages are likely eroded by serotype replacement.	Probable modest protection against 12 of the 13 serotypes included in the vaccine and uncertain protection against serotype 3. A good part of these advantages are likely eroded by serotype replacement.
Protection against otitis	Probable protection against the serotypes included in the vaccine. A large part of these advantages are likely eroded by serotype replacement.	Probable protection against the serotypes included in the vaccine, possibly against 6A and 19A. A large part of these advantages are likely eroded by serotype replacement.	Probable protection against the serotypes included in the vaccine, possibly against 6A and 19A. A large part of these advantages are likely eroded by serotype replacement.
Herd immunity	Herd immunity against 12 of the serotypes included in the vaccine, but not against serotype 3.	Herd immunity against 10 of the serotypes included in the vaccine but not against serotypes 3, 6A and 19A.	Probable herd immunity against 12 of the serotypes included in PCV13, but not against serotype 3, after the booster dose.

Table 6 Summary of the advantages and disadvantages of the different childhood vaccination schedules to prevent pneumococcal disease in Québec (continued)

Decision-making factor	2+1 PCV13	2+1 PCV10	Mixed schedule
Safety	Good	Good, but fewer local reactions	Good, but fewer local reactions with the first two doses
Cost	Probably the highest	Probably the lowest	Probably in between
Cost-effectiveness	Least favourable cost-effectiveness index	Intermediate cost-effectiveness index in many scenarios, and the most favourable in the assumption of non-inferiority of PCV10 compared to PCV13.	Most favourable cost-effectiveness index in many scenarios.
Acceptability	Strong	Weak	Intermediate
Feasibility	High	High	A little less
Compliance	High	Low in Canada, high worldwide	Low in Canada and worldwide

References

1. Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. Vaccine. 2005 Mar 31;23(19):2470–6.

2. Cohen O, Knoll M, O'Brien K, Ramakrishnan M, Constenla D, Privor-Dumm L, *et al*. Pneumococcal conjugate vaccine (PCV) product assessment. Baltimore (MD): Johns Hopkins Bloomberg School of Public Health [On line] https://www.jhsph.edu/research/centers-and-institutes/ivac/resources/pcv-product-assessment-april-25-2017.pdf (Page accessed August 9, 2017).

3. Boulianne N, De Wals P, Deceuninck G, Douville-Fradet M, Fortin E, Jetté L, *et al*. Impact du programme d'immunisation par le vaccin pneumococcique conjugué heptavalent (VPC-7), au Québec, Canada. Québec: Institut national de santé publique du Québec; 2007 Juin, 48 p.

4. Ministère de la Santé et des Services sociaux. Programme national de santé publique 2003-2012 - Mise à jour 2008. Québec: Direction générale de la santé publique, ministère de la Santé et des Services sociaux; 2008, 103 p.

5. Ministère de la Santé et des Services sociaux. Programme national de santé publique 2015-2025. Québec: Direction de la communication, ministère de la Santé et des Services sociaux; 2017, 85 p.

6. De Wals P, Boulianne N, Sevin E, Ouakki M, Deceuninck G, Guay M. Uptake of pneumococcal conjugate vaccine: methodological issues in measurement and impact of publicly funded programs. Can J Public Health. 2009 Nov;100(6):413–6.

7. Boulianne N, Audet D, Ouakki M, Dubé E, De Serres G, Guay M. Enquête sur la couverture vaccinale des enfants de 1 an et 2 ans au Québec en 2014. Québec: Institut national de santé publique du Québec; 2015, 151 p.

8. Lefebvre B, Longtin J, De Wals P, Deceuninck G, Douville-Fradet M. Programme de surveillance du pneumocoque : Rapport 2015. Laboratoire de santé publique du Québec; 2017, 27 p.

9. Zhou Z, Deceuninck G, Lefebvre B, De Wals P. Forecasting Trends in Invasive Pneumococcal Disease among Elderly Adults in Québec. Can J Infect Dis Med Microbiol J Can Mal Infect Microbiol Medicale. 2017;2017:4347206.

10. Anderson G, Deceuninck G, Zhou Z, Boucher FD, Bonnier Viger Y, Gilca R, *et al*. Hospitalisation for lower respiratory tract infection in children in the province of Québec, Canada, before and during the pneumococcal conjugate vaccine era. Epidemiol Infect. 2017 Aug 14;1–7.

11. Bruhn CAW, Hetterich S, Schuck-Paim C, Kürüm E, Taylor RJ, Lustig R, *et al*. Estimating the population-level impact of vaccines using synthetic controls. Proc Natl Acad Sci U S A. 2017 Feb 14;114(7):1524–9.

12. Berman S. Management of acute and chronic otitis media in pediatric practice. Curr Opin Pediatr. 1995 Oct;7(5):513–22.

13. Gould JM, Matz PS. Otitis media. Pediatr Rev. 2010 Mar;31(3):102–16.

14. Forgie S, Zhanel G, Robinson J, Comité des maladies infectieuses et d'immunisation de la SCP. La prise en charge de l'otite moyenne aiguë. Paediatr Child Health. 2009;14(7):461–4.

15. Madore DV, Klugman KP, Mäkelä PH, Siber GR. Pneumococcal vaccines: the impact of conjugate vaccine. In: American Society for Microbiology (ASM). Washington; 2008. p. 199–211.

16. Nahm MH, Klugman KP, Mäkelä PH, Siber GR. Pneumococcal vaccines: the impact of conjugate vaccine. In: American Society for Microbiology (ASM). Washington; 2008. p. 213–26.

17. Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, *et al*. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis. 2014 Sep;14(9):839–46.

18. Kohberger RC, Jokinen J, Siber GR. Establishing immune correlates of protection. In: Pneumococcal vaccines: the impact of conjugate vaccine. American Society for Microbiology (ASM). Washington; 2008. p. 339–45.

19. Wijmenga-Monsuur AJ, van Westen E, Knol MJ, Jongerius RMC, Zancolli M, Goldblatt D, *et al*. Direct Comparison of Immunogenicity Induced by 10- or 13-Valent Pneumococcal Conjugate Vaccine around the 11-Month Booster in Dutch Infants. PloS One. 2015;10(12):e0144739.

20. Urbancikova I, Prymula R, Goldblatt D, Roalfe L, Prymulova K, Kosina P. Immunogenicity and safety of a booster dose of the 13-valent pneumococcal conjugate vaccine in children primed with the 10-valent or 13-valent pneumococcal conjugate vaccine in the Czech Republic and Slovakia. Vaccine. 2017 Sep 12;35(38):5186–93.

21. Grimprel E, Laudat F, Patterson S, Baker SA, Sidhu MS, Gruber WC, *et al.* Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine (PCV13) when given as a toddler dose to children immunized with PCV7 as infants. Vaccine. 2011 Dec 6;29(52):9675–83.

22. Spijkerman J, Veenhoven RH, Wijmenga-Monsuur AJ, Elberse KEM, van Gageldonk PGM, Knol MJ, *et al*. Immunogenicity of 13-valent pneumococcal conjugate vaccine administered according to 4 different primary immunization schedules in infants: a randomized clinical trial. JAMA. 2013 Sep 4;310(9):930–7.

23. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, *et al*. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014 Oct 25;384(9953):1521–8.

24. Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, *et al*. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. Clin Infect Dis. 2015 Feb 1;60(3):333–7.

25. Niewiesk S. Maternal antibodies: clinical significance, mechanism of interference with immune responses, and possible vaccination strategies. Front Immunol. 2014;5:446.

26. Wood N, Siegrist C-A. Neonatal immunization: where do we stand? Curr Opin Infect Dis. 2011 Jun;24(3):190–5.

27. Ladhani SN, Andrews NJ, Southern J, Jones CE, Amirthalingam G, Waight PA, et al. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. Clin Infect Dis Off Publ Infect Dis Soc Am. 2015 Dec 1;61(11):1637–44.

28. Maertens K, Burbidge P, Van Damme P, Goldblatt D, Leuridan E. Pneumococcal Immune Response in Infants Whose Mothers Received Tdap Vaccination During Pregnancy. Pediatr Infect Dis J. 2017 Apr 10.

29. Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, *et al*. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet. 2006 Oct 28;368(9546):1495–502.

30. Jokinen J, Rinta-Kokko H, Siira L, Palmu AA, Virtanen MJ, Nohynek H, *et al*. Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children--a population-based study. PloS One. 2015;10(3):e0120290.

31. Naucler P, Galanis I, Morfeldt E, Darenberg J, Örtqvist Å, Henriques-Normark B. Comparison of the impact of PCV10 or PCV13 on invasive pneumococcal disease in equivalent populations. Clin Infect Dis. 2017: in press.

32. Deceuninck G, De Wals P, Bouliannne N, De Serres G. Effectiveness of Pneumococcal Conjugate Vaccine Using a 2+1 Infant Schedule in Québec, Canada. Pediatr Infect J. 2010 Feb 1;29(6):546–9.

33. Deceuninck G, De Serres G, Boulianne N, Lefebvre B, De Wals P. Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Québec, Canada. Vaccine. 2015 Apr 14;33(23):2684–9.

34. Tregnaghi MW, Sáez-Llorens X, López P, Abate H, Smith E, Pósleman A, *et al*. Efficacy of pneumococcal nontypable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) in young Latin American children: A double-blind randomized controlled trial. PLoS Med. 2014 Jun;11(6):e1001657.

35. Palmu AA, Saukkoriipi A, Snellman M, Jokinen J, Torkko P, Ziegler T, *et al*. Incidence and etiology of community-acquired pneumonia in the elderly in a prospective population-based study. Scand J Infect Dis. 2014 Apr;46(4):250–9.

36. Domingues CMAS, Verani JR, Montenegro Renoiner EI, de Cunto Brandileone MC, Flannery B, de Oliveira LH, *et al*. Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study. Lancet Respir Med. 2014 Jun;2(6):464–71.

37. Verani JR, Domingues CMAS, de Moraes JC, Brazilian Pneumococcal Conjugate Vaccine Effectiveness Study Group. Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease. Vaccine. 2015 Nov 17;33(46):6145–8.

38. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, *et al*. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis. 2015 Mar;15(3):301–9.

39. Guevara M, Barricarte A, Torroba L, Herranz M, Gil-Setas A, Gil F, *et al*. Direct, indirect and total effects of 13-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in children in Navarra, Spain, 2001 to 2014: cohort and case-control study. Euro Surveill Bull Eur Sur Mal Transm Eur Commun Dis Bull. 2016;21(14).

40. Van der Linden M, Falkenhorst G, Perniciaro S, Fitzner C, Imöhl M. Effectiveness of Pneumococcal Conjugate Vaccines (PCV7 and PCV13) against Invasive Pneumococcal Disease among Children under Two Years of Age in Germany. PloS One. 2016;11(8):e0161257.

41. Weinberger DM, Grant LR, Weatherholtz RC, Warren JL, O'Brien KL, Hammitt LL. Relating Pneumococcal Carriage Among Children to Disease Rates Among Adults Before and After the Introduction of Conjugate Vaccines. Am J Epidemiol. 2016 Jun 1;183(11):1055–62.

42. Su W-J, Lo H-Y, Chang C-H, Chang L-Y, Chiu C-H, Lee P-I, *et al*. Effectiveness of Pneumococcal Conjugate Vaccines of Different Valences Against Invasive Pneumococcal Disease Among Children in Taiwan: A Nationwide Study. Pediatr Infect Dis J. 2016 Apr;35(4):e124–33.

43. Savulescu C, Krizova P, Lepoutre A, Mereckiene J, Vestrheim DF, Ciruela P, *et al*. Effectiveness of higher valency conjugate vaccines on invasive pneumococcal disease in Europe : preliminary results of SpIDnet multicentre project. Poster presentation. 9th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD 2014), Hyderabad, India, March 9-13, 2014.

44. Shigayeva A, Rudnick W, Green K, Tyrrell G, Demczuk WHB, Gold WL, *et al*. Association of serotype with respiratory presentations of pneumococcal infection, Ontario, Canada, 2003-2011. Vaccine. 2016 Feb 3;34(6):846–53.

45. Kilpi J. Effectiveness of pneumococcal Haemophilus influenzae protein D conjugate vaccine against radiologically confirmed pneumonia. Poster presentation. 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington, DC, September 5-9, 2014.

46. Black SB, Shinefield HR, Ling S, Hansen J, Fireman B, Spring D, *et al*. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect J. 2002 Sep;21(9):810–5.

47. Bonten MJM, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, *et al*. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015 Mar 19;372(12):1114–25.

48. Berglund J, Vink P, Tavares Da Silva F, Lestrate P, Boutriau D. Safety, immunogenicity, and antibody persistence following an investigational Streptococcus pneumoniae and Haemophilus influenzae triple-protein vaccine in a phase 1 randomized controlled study in healthy adults. Clin Vaccine Immunol CVI. 2014 Jan;21(1):56–65.

49. Zhou Z, Gilca R, Deceuninck G, Boucher FD, Charest H, De Wals P. Predictors of hospitalization for lower respiratory tract infection in children aged <2 years in the province of Québec, Canada. Epidemiol Infect. 2015 Sep 18;144(5):1035–44.

50. Vesikari T, Forsten A, Bianco V, Van der Wielen M, Miller JM. Antibody persistence up to 5 years after vaccination of toddlers and children between 12 months and 10 years of age with a quadrivalent meningococcal ACWY-tetanus toxoid conjugate vaccine. Hum Vaccines Immunother. 2016;12(1):132–9.

51. Ben-Shimol S, Givon-Lavi N, Leibovitz E, Raiz S, Greenberg D, Dagan R. Near-elimination of otitis media caused by 13-valent pneumococcal conjugate vaccine (PCV) serotypes in southern Israel shortly after sequential introduction of 7-valent/13-valent PCV. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014 Dec 15;59(12):1724–32.

52. Gisselsson-Solen M. Trends in Otitis Media Incidence After Conjugate Pneumococcal Vaccination; A National Observational Study. Pediatr Infect Dis J. 2017 Nov;36(11):1027-1031

53. Bogaert D, van Belkum A, Sluijter M, Luijendijk A, de Groot R, Rümke HC, *et al*. Colonisation by Streptococcus pneumoniae and Staphylococcus aureus in healthy children. Lancet Lond Engl. 2004 Jun 5;363(9424):1871–2.

54. Hausdorff WP, Hanage WP. Interim results of an ecological experiment - Conjugate vaccination against the pneumococcus and serotype replacement. Hum Vaccines Immunother. 2016;12(2):358–74.

55. Sings H. Impact of pneumococcal conjugate vaccines on serotype 19A nasopharyngal carriage. Poster presentation. European Society for Pediatric Infectious Diseases Conference (ESPID), Madrid (Spain) May 5, 2017.

56. Pastor P. A systematic review of pneumococcal conjugate vaccine (PCV) impact on acute otitis media (OM) and nasopharyngeal carriage (NP) due to nontypeable Haemophilus influenza (NTHi). Poster presentation. European Society for Pediatric Infectious Diseases Conference (ESPID), Madrid (Spain) May 5, 2017.

57. Nicholls TR, Leach AJ, Morris PS. The short-term impact of each primary dose of pneumococcal conjugate vaccine on nasopharyngeal carriage: Systematic review and meta-analyses of randomised controlled trials. Vaccine. 2016 Feb 3;34(6):703–13.

58. Steens A, Bergsaker MAR, Aaberge IS, Rønning K, Vestrheim DF. Prompt effect of replacing the 7-valent pneumococcal conjugate vaccine with the 13-valent vaccine on the epidemiology of invasive pneumococcal disease in Norway. Vaccine. 2013 Dec 16;31(52):6232–8.

59. Waight PA, Andrews NJ, Ladhani SN, Sheppard CL, Slack MPE, Miller E. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infect Dis. 2015 May;15(5):535–43.

60. Knol MJ, Wagenvoort GHJ, Sanders EAM, Elberse K, Vlaminckx BJ, de Melker HE, *et al*. Invasive Pneumococcal Disease 3 Years after Introduction of 10-Valent Pneumococcal Conjugate Vaccine, the Netherlands. Emerg Infect Dis. 2015 Nov;21(11):2040–4.

61. Rudnick W, Liu Z, Shigayeva A, Low DE, Green K, Plevneshi A, *et al*. Pneumococcal vaccination programs and the burden of invasive pneumococcal disease in Ontario, Canada, 1995-2011. Vaccine. 2013 Dec 2;31(49):5863–71.

62. Destefano F, Pfeifer D, Nohynek H. Safety profile of pneumococcal conjugate vaccines: systematic review of pre- and post-licensure data. Bull World Health Organ. 2008 May;86(5):373–80.

63. Croxtall JD, Keating GM. Pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix; PHiD-CV). Paediatr Drugs. 2009;11(5):349–57.

64. Prymula R, Schuerman L. 10-valent pneumococcal nontypeable Haemophilus influenzae PD conjugate vaccine: Synflorix. Expert Rev Vaccines. 2009 Nov;8(11):1479–500.

65. Bryant KA, Block SL, Baker SA, Gruber WC, Scott DA, PCV13 Infant Study Group. Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. Pediatrics. 2010 May;125(5):866–75.

66. Nunes MC, Madhi SA. Review on the immunogenicity and safety of PCV-13 in infants and toddlers. Expert Rev Vaccines. 2011 Jul;10(7):951–80.

67. Thompson A, Gurtman A, Patterson S, Juergens C, Laudat F, Emini EA, *et al*. Safety of 13-valent pneumococcal conjugate vaccine in infants and children: meta-analysis of 13 clinical trials in 9 countries. Vaccine. 2013 Oct 25;31(45):5289–95.

68. Ruiz-Aragón J, Márquez Peláez S, Molina-Linde JM, Grande-Tejada AM. Safety and immunogenicity of 13-valent pneumococcal conjugate vaccine in infants: a meta-analysis. Vaccine. 2013 Nov 4;31(46):5349–58.

69. Littlejohn ES, Clothier HJ, Perrett KP, Danchin M. Surveillance of adverse events following the introduction of 13-valent pneumococcal conjugate vaccine in infants, and comparison with adverse events following 7-valent pneumococcal conjugate vaccine, in Victoria, Australia. Hum Vaccines Immunother. 2015;11(7):1828–35.

70. Trück J, Lazarus R, Jonsdottir I, Klugman KP, Pollard AJ. Pneumococcal polysaccharide vaccine efficacy and routine use of conjugate vaccines in infants: there is no need for a vaccine program in older adults at present. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012 Dec;55(11):1577–9; author reply 1579–81.

71. Walker DG, Hutubessy R, Beutels P. WHO Guide for standardisation of economic evaluations of immunization programmes. Vaccine. 2010 Mar 8;28(11):2356–9.

72. Oligbu G, Collins S, Sheppard CL, Fry NK, Slack M, Borrow R, *et al*. Childhood Deaths Attributable to Invasive Pneumococcal Disease in England and Wales, 2006-2014. Clin Infect Dis. Jul 15;65(2):308-314.

73. Jit M. The risk of sequelae due to pneumococcal meningitis in high-income countries: a systematic review and meta-analysis. J Infect. 2010 Jul;61(2):114–24.

74. Morrow A, De Wals P, Petit G, Guay M, Erickson LJ. The burden of pneumococcal disease in the canadian population before routine use of the seven-valent pneumococcal conjugate vaccine. Can J Infec Med Microb. 2007 Mar;18(2):121–7.

Appendix 1

Summary of declarations of interest

Summary of declarations of interest by the members of the Comité sur l'immunisation du Québec (CIQ)

NOVEMBER 2017

The Institut national de santé publique du Québec (INSPQ) asked the members of the Comité sur l'immunisation du Québec (CIQ) to produce a supplementary declaration of any potential conflict of interest situations in the past three years related to the choice of vaccines for the prevention of pneumococcal disease in children.

1 No conflicting interests declared:

François Boucher, Marjolaine Brideau, Dominique Biron, Nicholas Brousseau, Ngoc Yen Giang Bui, Hélène Gagné, Maryse Guay, Catherine Guimond, Patricia Hudson, Monique Landry, Richard Marchand, Céline Rousseau, Caroline Quach, Chantal Sauvageau, Bruno Turmel.

2 Research grants obtained as principal investigator or co-investigator connected with private corporations whose products or activities are related to pneumococcal vaccination:

Alex Carignan: Pfizer;

Gaston De Serres: Pfizer, GSK;

Philippe De Wals: Pfizer, GSK;

Marc Dionne: GSK, Pfizer, Merck;

Vladimir Gilca: Pfizer;

Bruce Tapiéro: GSK, Merck.

3 Consulting/speaking fees or travel costs (TC) received from private corporations whose products or activities are related to pneumococcal vaccination:

Julie Bestman-Smith: Consulting/speaking fees paid to her organization: Merck, Pfizer, TC for conferences: Merck;

Alex Carignan: TC for consulting services: Pfizer;

Philippe De Wals: TC for speaking engagement: Novartis, pharmaceutical consortium, TC for consulting services: GSK, Pfizer;

Marc Lebel: Fees and TC for speaking engagement: Pfizer, Merck, consulting fees: GSK, Pfizer, TC for consulting services GSK.

Appendix 2

Characteristics of cases of serotype 3 invasive pneumococcal disease included in the directory of reportable diseases in children under age five in Québec and vaccinated with ≥ 1 dose of PCV13, 2011–2015

Characteristics of cases of serotype 3 invasive pneumococcal disease included in the directory of reportable diseases in children under age five in Québec and vaccinated with ≥ 1 dose of PCV13, 2011–2015

Year	Age in months	Clinical presentation	Risk factor	PCV13 doses	Age 1st dose (days)	Age 2nd dose (days)	Age 3rd dose (days)	Age 4th dose (days)	Time to final dose (days)
2012	4	Meningitis		1	63				67
2012	11	AOM	West syndrome	2	108	152			204
2014	24	AOM	Encephalopathy	3	73	136	366		392
2014	27	Bacteremia		3	72	156	389		438
2015	28	Empyema	(Extremely premature infant)	3	59	122	374		483
2015	32	Empyema		3	71	153	394		604
2015	48	Bacteremia	Immunosuppressant drug	4	64	127	182	371	1,095

Source: Epidemiological survey on invasive pneumococcal disease in children under age five in Québec, INSPQ.

Appendix 3

Characteristics of cases of serotype 19A invasive pneumococcal disease included in the directory of reportable diseases in children under age five in Québec and vaccinated with ≥ 1 dose of PCV13, 2011–2015

Characteristics of cases of serotype 19A invasive pneumococcal disease included in the directory of reportable diseases in children under age five in Québec and vaccinated with ≥ 1 dose of PCV13, 2011–2015

Year	Age in months	Clinical presentation	Risk factor	PCV13 doses	Age 1st dose (days)	Age 2nd dose (days)	Age 3rd dose (days)	Age 4th dose (days)	Time to final dose (days)
2011	2	Bacteremia		1	62				20
2011	9	AOM		2	61	127			175
2011	11	Pneumonia		2	57	116			220
2011	12	Mastoiditis		2	46	109			279
2012	2	Bacteremia	Northern region	1	71				16
2012	8	Meningitis		2	66	137			115
2012	8	AOM		2	64	123			137
2012	9	Mastoiditis		3	77	113	198		106
2012	10	AOM		2	90	153			168
2012	10	AOM		2	65	128			179
2012	10	Pneumonia		2	75	141			171
2012	10	Bacteremia		2	68	123			203
2012	11	AOM		2	65	127			208
2012	16	Empyema		3	54	109	370		131
2013	9	AOM		2	64	125			154
2013	10	AOM		2	64	127			180
2013	11	Mastoiditis		2	64	119			232
2013	12	Mastoiditis		2	62	125			252
2013	14	Bacteremia	Laryngomalacia	2	62	124			306
2014	9	AOM		2	67	125			158
2014	10	AOM		2	62	124			207
2014	24	Empyema		3	62	125	379		372
2014	30	Empyema	Carrier of the sickle cell trait	3	67	131	380		551
2015	8	Pneumonia		2	60	123			147
2015	16	AOM	Northern region	4	67	133	189	441	62
2015	24	Pneumonia		3	62	118	384		362
2015	37	Pneumonia	Congenital immunodeficiency and transplant	2	74	120			1013

Source: Epidemiological survey on invasive pneumococcal disease in children under age 5 in Québec, INSPQ.

Publication Nº: 2379

Centre d'expertise
et de référence

www.inspq.qc.ca

Institut national
de santé publique
Québec